REMARKS

Claims 13-15 and 17-40 are all the claims pending in the application. Claims 1-12 have been canceled without prejudice or disclaimer. In addition, Applicants expressly reserve the right to file a divisional application directed to claims 1-12 at a later date.

Claim 13 has been amended based on, for example, page 7, lines 15-17 and page 8, lines 6-14 of the specification. New claims 31-40 have been added based on, for example, original claims 2-12.

Entry of the above amendments is respectfully requested.

I. Information Disclosure Statement

It is noted that the Examiner crossed out the references listed on the PTO/SB/08 A & B (modified) filed with the Information Disclosure Statement of January 10, 2006. It is submitted that the references should have been received from the International Bureau. However, the references cited in the Information Disclosure Statement are submitted herewith along with a PTO/SB/08 A & B (modified). The Examiner is respectfully requested to return a signed and initialed copy of the PTO/SB/08 form indicating that the references have been considered and made of record.

II. Response to Rejection of Claims 13-16 under 35 U.S.C. § 112, first paragraph

Claims 13-16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of making proteins from recombinant DNA constructs that are uniformly isotopically labeled on C, H, and O atoms, does not reasonably provide enablement for making isotopically labeled biomolecules of any sort other than proteins or for making non-recombinant isotopically labeled proteins or for making recombinant proteins labeled with isotopes other than ^{13}C, ^{2}H and/or ^{15}N.

Applicants respectfully traverse and submit that the specification does enable one of skill in the art to make and/or use the claimed invention.

Nonetheless, without acquiescing the merits of the rejection, claim 13 has been amended to recite "a method for producing a biomolecule, whereby substantially all atoms in the biomolecule, for at least one of H, C or N, are isotopically labeled". Claim 13 has also been amended to the production of "a biomolecule that is naturally synthesized by the mammalian or insect cells, or a biomolecule that is a mammalian polypeptide or nucleic acid produced as a result of genetic engineering of the mammalian or insect cells". Support for this amendment can be found, for example, at page 8, lines 6-14 of the specification. Accordingly, the production of toxic compounds, such as cyanide, is excluded from the scope of claim 13.

Claim 13 has been further amended to the production of mammalian protein so as to exclude the production of bacterial proteins in mammalian or insect cells. In this regard, it is submitted that it is generally known in the art that mammalian and insect cells are very capable of producing mammalian proteins.

Finally, claim 13 has been amended to growing cells actually producing the biomolecule. It is submitted that there should be no difference between the enablement of recombinant proteins and endogenous proteins of the insect or mammalian cells as both recombinant and endogenous proteins are synthesized from the same pool of charged tRNAs in the cells. Furthermore, Example 6 of the present specification shows that both the insect or mammalian cells grow at the doubling times comparable to those in commercially available serum-free media. This as an indication of the absence of stress-conditions, on the basis of which it is submitted that there is no reason to assume that the cells would not express their normal repertoire of endogenous proteins.

In view of the above, it is requested that the rejection be withdrawn.

III. Response to Rejection of Claims 13-16 under 35 U.S.C. § 112, second paragraph

Claims 13-16 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

Applicants respectfully traverse the rejection.

It is respectfully submitted that, a currently written, the claims are clear and definite. Nonetheless, without acquiescing the merits of the rejection, claim 13 has been amended to recite "95% or more" instead of "substantially all" the atoms are isotopically labeled. In addition, amended claim 13 requires the biomolecule actually being produced.

Claim 14 has been amended to delete "soluble protein" as it already clear that all proteins other than membrane proteins are covered by claim 13.

Claim 15 has been amended to positively require that the protein is produced from the expression vector.

In view of the above, withdrawal of the rejections is respectfully requested.

IV. Response to Rejection of Claims 13-16 under 35 U.S.C. § 102(b)

Claims 13-16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hansen et al. (1992, Biochemistry 31: 12713-12718).

Applicants respectfully traverse the rejection.

Claim 13 is directed to a method for producing a biomolecule, whereby about 95% or more of the atoms in the biomolecule, for at least one of H, C or N, are isotopically labelled, the method comprising the steps of: (a) growing a culture of mammalian or insect cells producing the biomolecule under conditions conducive to the production of the biomolecule, in a nutrient medium produced by: (i) growing an organism on a mineral medium which supports growth of the organism, whereby in the medium about 95% or more of the assimilable atoms, for at least

one of H, C or N, are isotopically labelled, to produce labelled biomass; (ii) autolysing the biomass of the organism grown as in (i) to produce an autolysate; and, (iii) composing the nutrient medium by combining the autolysate as obtained in (ii) with further components necessary for growth of the mammalian or insect cells; and (b) recovery of the biomolecule, whereby the biomolecule is a molecule that is naturally synthesized by the mammalian or insect cells, or the biomolecule is a mammalian polypeptide or nucleic acid produced as a result of genetic engineering of the mammalian or insect cells.

The media of Hansen are made by acid hydrolysis of isotopically labeled biomass of bacteria or algae, which yields mostly free amino acids that are purified by cation exchange chromatography and filtration through a 500 Mw cutoff membrane. *See* page 12714 and the penultimate paragraph of the right-hand column at page 12715.

The media of the present invention comprise an autolysate as an important feature. This autolysate comprises, in addition to free amino acids, polypeptides, nucleotides, proteins, glycogen, sugars, B-vitamins, organic acids, lipids (*cf* page 6, lines 12-14 of the specification), and oligopeptides (*cf* page 27, lines 22-24, and page 41, lines 1-4 of the specification). The autolysates of the present invention are not purified by cation exchange and they are not filtered through a 500 Mw cutoff membrane; otherwise the components other than free amino acids would not be present. Therefore, a structural difference between the media of Hansen and the media used in the presently claimed method is the presence of labeled components with a Mw higher than 500, in particular oligopeptides.

In addition, it is submitted that Hansen teaches away from using hydrolysates that are not obtained by acid hydrolysis and that are not filtered with a 500 Mw cutoff. The bottom paragraph of page 12715 of Hansen describes that media prepared with amino acids from an enzymatic hydrolysate of labeled algal biomass "were unable to support cell growth". The

penultimate paragraph of the right-hand column at page 12715 describes amino acid obtained from acid hydrolysis that "passage of the amino acids through a 500 molecular weight cutoff membrane improved cell growth". Both statements clearly teach away from using an autolysate as claimed in the present invention.

Hence, it is submitted that Hansen does not anticipate claim 13.

For at least the foregoing reasons, it is submitted that claim 13 is patentable over Hansen. Additionally, claims 14-15 and 31-40, which depend from claim 13, are also patentable for at least the same reasons as claim 13.

Accordingly, withdrawal of the rejection is respectfully requested.

V. Conclusion

In view of the above, reconsideration and allowance of claims 13-15 and 17-40 is respectfully requested. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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